IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

Juha-Matti SAVOLA et al.

Serial Number: 10/534,091 Group Art Unit: 1618

Filing Date: May 6, 2005 Examiner: Gembeh, Shirley V.

For: OROMUCOSAL FORMULATION AND PROCESS FOR PREPARING THE SAME

REQUEST FOR RECONSIDERATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450 December 30, 2009

Sir:

In response to the Official Action mailed September 11, 2009, a RCE and Petition for a one month Extension of Time being submitted herewith, please reconsider this application in view of the following remarks. Claims 23 and 25-33 are pending.

The 35 U.S.C. § 103(a) rejection of claims 23, 25-29 and 31-33 over Huupponen et al., Clin.Pharmacol.Ther., 58, 506-11 (1995) in view of U.S. Patent No. 5,498,623 to Karjalainen et al. is traversed. The claimed method requires a formulation containing fipamezole [4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole or its acid salt] to be administered to a patient by oromucosal administration, defined as absorption via oral mucosa.

The applicants have discovered that the problem of QTc prolongation (encountered when fipamezole is orally administered)

is avoided when fipamezole is oromucosally administered. See Example 8 of the application and the Declaration Pursuant to 37 C.F.R. § 1.132 filed February 17, 2009.

The applicants concede the combination of Huupponen et al. and Karjalainen et al. raises a *prima facie* case of obviousness against the claimed method. However, the claimed method produces an unexpected result (the *absence* of QTc prolongation) which cannot be predicted from the cited references and which overcomes the *prima facie* case.

The points made in the previous Amendment are repeated and incorporated by reference herein. Briefly, Huupponen et al. and Karjalainen et al. both fail to disclose anything regarding QTc prolongation. However, one of ordinary skill in the art, aware that oral administration of fipamezole causes a dose-dependent prolongation of the QTc interval, would expect an equivalent or longer QTc prolongation if fipamezole was oromucosally administered because of Huupponen et al.'s teaching regarding the increased bioavailability of atipamezole (a fipamezole analog) when oromucosally administered. The absence of any QTc prolongation when fipamezole is oromucosally administered is thus unexpected and

surprising. See the detailed points made in the previous Amendment,

A Rule 132 declaration by Dr. Jurg P. Seiler ("Seiler Declaration") is attached as additional *evidence* of the unexpected and surprising result achieved by the claimed method. Dr. Seiler, an independent toxicology expert, reviewed the application and the cited prior art, and concluded the absence of QTc prolongation when fipamezole is oromucosally administered could not have been predicted from Karjalainen et al. or Huupponen et al. See paragraph No. 12 of the Seiler Declaration.

Dr. Seiler concluded the inventors' discovery that oromucosal administration of fipamezole does not result in QTc prolongation is unexpected and surprising because (1) the prolongation is dose-dependent when fipamezole is orally administered, and (2) equivalent or greater bioavailability can be expected when fipamezole is oromucosally administered. See paragraph No. 13 of the Seiler Declaration.

The Examiner's attention is also drawn to the fact that Dr. Seiler has never seen a case like this before, despite the fact that QTc prolongation is a recognized problem, as evidenced by the FDA's Guidelines for nonclinical evaluation of a compound's

potential to prolong the QTc interval, and the withdrawal of several pharmaceutical compounds from the market. Yet Dr. Seiler testifies he is unaware of any other compound in which a change in the mode of administration has eliminated a QTc prolongation problem. See paragraph No. 13 of the Seiler Declaration. This is persuasive evidence that the result achieved by the claimed method (lack of QTc prolongation) is unexpected and surprising.

Finally, the Patent Office arguments for maintaining this obviousness rejection are without merit. Huupponen et al.'s disclosure that oromucosal administration of atipamezole did not affect heart rate (measured in beats/minute) is irrelevant to whether atipamezole does (or does not) prolong the QTc interval (measured in milliseconds). Paragraph No. 12 of the Seiler Declaration points out that QTc prolongation can be induced at an unchanged heart rate, and that QTc is a value corrected for changes in heart rate, and is thus independent of any heart rate change.

The Patent Office argument that the FDA's Guidance for Industry is irrelevant because it was published after the application's priority date is also without merit. Evidence of unexpected results is not limited to information in the applicants' specification or the state of the art at the time of application.

Knoll Pharm. Co., Inc. v. Teva Pharm. USA, Inc., 367 F.3d 1381, 70 USPQ2d 1957 (Fed. Cir. 2004).

The Patent Office argument that fipamezole's therapeutic activity is inherent is also without merit. First, the claims recite a method of administration of fipamezole, not the admittedly known compound itself. Karjalainen et al. fails to expressly or inherently disclose oromucosal administration of fipamezole. Second, an obviousness rejection cannot be based on what is unknown. The applicants' *initial* discovery was fipamezole's inherent property to prolong the QTc interval when orally administered. Their subsequent discovery was fipamezole's inherent property not to prolong the QTc interval when oromucosally administered. Neither inherent property of fipamezole was previously known to those of ordinary skill in the art. Yet once the initial discovery was made, the applicants' subsequent discovery was unexpected and surprising for the reasons set forth in the Seiler Declaration.

Reconsideration and withdrawal of the obviousness rejection of claims 23, 25-29 and 31-33 over Huupponen et al. in view of Karjalainen et al. are respectfully requested.

The 35 U.S.C. § 103(a) rejection of claims 23 and 25-33 over Huupponen et al. and Karjalainen et al., further in view of U.S. Patent No. 6,413,988 to de Proost, is traversed for the same reasons previously discussed. De Proost is not directed to α_2-adrenergic receptor antagonists, and does not disclose any information concerning oromucosal vs. oral administration of fipamezole. Accordingly, the additional disclosure of this secondary reference does not detract from the unexpected and surprising result achieved by the claimed method of administration. Reconsideration and withdrawal of the obviousness rejection of claims 23 and 25-33 over Huupponen et al. and Karjalainen et al., further in view of de Proost, are respectfully requested.

It is believed this application is in condition for allowance. Reconsideration and withdrawal of the obviousness rejections of claims 23 and 25-33, and issuance of a Notice of Allowance directed to those claims, are respectfully requested. The Examiner is urged to telephone the undersigned should she believe any further action is required for allowance.

The fees for the RCE and Extension of Time are being paid electronically today. It is not believed any additional fee is required for entry and consideration of this Request for

Reconsideration. Nevertheless, the Commissioner is authorized to charge Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

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Enclosures:
- Petition of Extension of Time
- Request for Continued Examination
- Declaration Pursuant to 37 C.F.R. § 1.132
- Supplemental Information Disclosure Statement